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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: HAN, ZHENGXU
	: KRISHNAMURTHY, DHILEEPKUMAR
	: SENANAYAKE, CHRIS HUGH
	: LU, ZHI-HUI
Assignee	: Apsinterm, LLC
Serial No.	: 10/508,941
Filed	: March 2, 2005
For	: Method of Preparing Amine Stereoisomers
Art Unit	: 1626
Examiner	: Freistein, Andrew B.
Docket No.	: 00314/US1
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Commissioner for Patents
P.O. Box 1450
Alexandria
VA 22313-1450
United States

Sir:

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Martin A. Hay & Co.

13 Queen Victoria Street
Macclesfield
Cheshire SK11 6LP
UNITED KINGDOM

Tel: (+44) 1625 500057
Fax: (+44) 1625 500058

E-mail: martinahay@martin-a-hay.com

FACSIMILE TRANSMITTAL SHEET

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To: Attn: Group Art Unit 1626
USPTO

FAX Number: 001 703 872 9306

From: Martin A Hay

FAX Number: (44) 1625 500058

Acknowledgment Requested: Yes No

Message:

Re: Appln Serial No 10/508,941
Applicants: Han, Zhengxu et al
Our Ref: 00314/US1

Response to Office Communication of August 22, 2005.

This communication is being filed in response to the Office Communication of August 22, 2005.

Restriction under 35 U.S.C. § 121 and 375

The Examiner requires restriction of the application to one of the following Groups of inventions:-

Group I: Claims 1 to 32
Group II: Claims 33 and 38
Group III: Claims 39-42
Group IV: Claims 43 to 45

Applicants hereby elected to prosecute the invention of Group I, Claims 1 to 32. The election is made without traverse.

Election of Species under 37 C.F.R. 1.146

The Examiner has requested the election of a single compound.

It is understood that the Examiner is requiring a election of species of the invention under 37 C.F.R. 1.146, and that the examination will only be restricted to this species if no claim to the genus is found to be allowable.

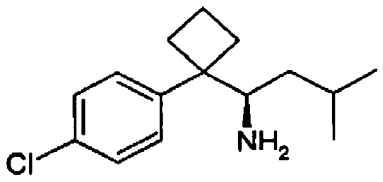
Although Applicants have described their invention primarily with respect to a process for making stereoisomers of the compound sibutramine, it is respectfully submit that they have actually invented a general process for preparing amine stereoisomers. The terms used in Claim 1 are believed to properly define this process. In this connection, the Examiner's attention is drawn to co-pending application serial number 10/120,541, cited in Applicant's information disclosure statement, which claims a related process invention in broad

terms. This related invention has been searched broadly by the Examiner handling it. Applicants very much hope that it will prove possible for the Examiner to conduct a similarly broad search in the present application.

Applicants hereby elect the species of the invention described generally in Scheme 6 on pages 36 to 37 and specifically in Example 5.16 and Scheme 13, on pages 50 to 51. This scheme depicts a process for preparing the amine stereoisomer (R)-didesmethylsibutramine, which could be alkylated to afford (R)-sibutramine (see formulae in Schemes 1 and 2 on page 2).

Referring to Schemes 6 and 13 and to Claim 1, the process described in Schemes 6 and 13 maps to Claim 1 as follows:-

A method of preparing an amine stereoisomer:-

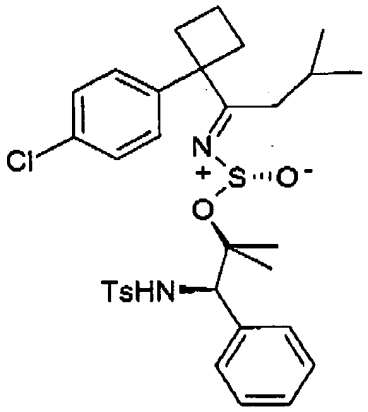


(R)-didesmethylsibutramine.

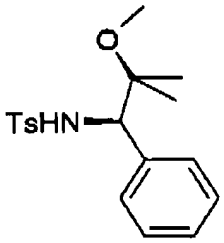
which comprises stereoselectively reducing:-

using e.g. $NaBH_4$ as reducing agent

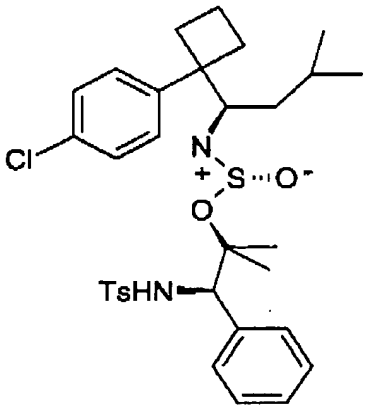
a sulfinylimine:-



that bears on the sulfinyl group a residue of an alcohol:-



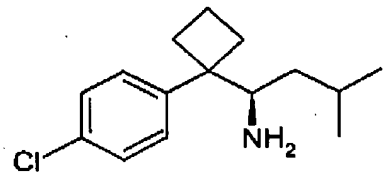
to afford a sulfinylamine stereoisomer:-



followed by contacting the sulfinylamine stereoisomer with a reagent suitable for the cleavage of a sulfur-nitrogen bond:-

an acid, e.g. HCl

to afford an amine stereoisomer:-



It may be helpful to the Examiner to appreciate that in the elected species and generally in preferred embodiments of the invention, the invention effectively makes use of the stereochemistry in a beta-amino alchohol stereoisomer to set the stereochemistry in an amine product. The process proceeds via a chiral 1,2,3-oxathiazolidine-S-oxide. If the Examiner looks at a formula for a 1,2,3-oxathiazolidine-S-oxide (e.g. formula 3 on page 29), he will see that the oxa and aza parts are derived from the hydroxy and amino parts of the beta-amino alcohol.

The following dependent claims 2 to 30 also read on the elected species:-

2 - sulfinylimine is a sulfinylimine stereoisomer

3 - residue of alcohol is in stereoisomeric form

4 - residue of an alcohol is residue of an N-substituted beta-amino alcohol

5 - alcohol maps to formula in wherein A_1 is $-L-R_{7a}$ in which -L- represents $-SO_2-$ and R_{7a} represents substituted aryl (p-toluene), A_2 is O, R_8 is hydrogen, R_9 is phenyl, R_{10} is hydrogen and R_{11} is hydrogen

6 - A_2 is O

7 - R_8 is hydrogen, R_9 is phenyl, R_{10} is hydrogen and R_{11} is hydrogen

8 - R_7 is $-SO_2-R_{7a}$ in which R_{7a} is (6-10C)aryl (phenyl) substituted by (1-4C)alkyl (methyl).

9 - R_7N is residue of an optionally N-substituted 1-amino-1-phenyl-2-methyl-2-propanol

10 - sulfinylimine has been prepared by contacting an iminometal (with a 1,2,3-oxathiazolidine-S-oxide - see scheme 8 and Example 5.8.1 on pages 41-42

11 - 1,2,3-oxathiazolidine-S-oxide is a compound of formula 3 wherein A_1 is $-L-R_{7a}$ in which -L- represents $-SO_2-$ and R_{7a} represents substituted aryl (p-toluene), A_2 is O, R_8 is hydrogen, R_9 is phenyl, R_{10} is hydrogen and R_{11} is hydrogen

12 - 1,2,3-oxathiazolidine-S-oxide is the first of the depicted stereoisomers

13 - amine stereoisomer is a compound of formula 5 in which R_5 and R_6 are each substituted alkyl and R_{12} and R_{13} are each hydrogen

14 - A_2 is O

15 - R_5 and R_6 are each substituted alkyl, the 1,2,3-oxathiazolidine-S-oxide is a compound of formula 3, and the sulfinylimine stereoisomer is of formula 4.

16 - R_{12} and R_{13} are both hydrogen

17 - 1,2,3-oxathiazolidine-S-oxide has been prepared by reacting an optionally N-substituted beta-amino alcohol (N-tosyl-1-amino-1-phenyl-2-methyl-2-propanol) with a thionyl halide (thionyl chloride) - see e.g. scheme 3 on page 32

18 -Amine stereoisomer product of elected process species could be alkylated to afford sibutramine (see structure on page 2).

19 - amine stereoisomer is covered by formula 7

20 - amine stereoisomer is covered by formula 14

21 - R_{15} and R_{16} are both hydrogen

22 - metal imine is as depicted

23 - 1,2,3-oxathiazolidine-S-oxide is first depicted formula

24 - sulfinylimine is reduced using a hydride reducing agent (e.g. $NaBH_4$)

25 - hydride reducing agent is $NaBH_4$

26 - cleavage reagent is an acid (HCl)

27 - acid is HCl

28 - cleavage of sulfur-nitrogen bond also affords an optionally N-substituted beta-aminoalcohol that may be recycled

29 - use of stereoselective reducing agent instead of $NaBH_4$

30 - amine stereoisomer is (R)-sibutramine - if amine stereoisomer product is alkylated as in Claim 18

Dependent claims 31 and 32 do not read on the elected species of Scheme 13. They are directed to embodiments of the invention claimed in Claim 1 in which a sulfinylimine stereoisomer is reacted with a source of a nucleophile instead of being reduced. The Examiner will appreciate that the claims require amendment, because the words "sulfinylamine stereoisomer" should read "sulfinylimine stereoisomer".

Conclusion

In response to the Examiner's restriction requirement, Applicants have elected to prosecute the invention of Group I, Claims 1 to 32, without traverse.

In response to the Examiner's request for an election of species, which it is understood is being made under 37 C.F.R. 1.146, Applicants have elected the species of the claimed process described in Example 5.16, which affords the amine stereoisomer(R)-didesmethylsibutramine. Applicants have provided a detailed analysis of how each dependent claim does or does not read on this elected species. It is understood that the election of species is required for examination purposes only, and that the application will only be restricted to this species if no generic claim is found to

be allowable. In this connection, it is respectfully submitted that the present invention provides a process for preparing amine stereoisomers in general, and that the generic claims progressively further define the features of this process. It is very much hoped that the Examiner will be able to extend his search beyond a process for making (R)-didesmethylsibutramine to a process for making amine stereoisomers generically as in claim 1 or at least as in one of the dependent generic claims.

Communication by Telephone

The undersigned's office is located in the United Kingdom, and hence the Examiner may have difficulty contacting him from the USPTO by telephone. If the Examiner wishes to speak with the undersigned by telephone, he can contact the undersigned by e-mail at martinahay@martin-a-hay.com.

Respectfully submitted,

Hay, Martin Alexander
Agent for Applicants
Registration No. 39,459
Phone: 011 44 1625 500057
e-mail: martinahay@martin-a-hay.com

Customer No. 024330
[Martin A. Hay & Co.,
13 Queen Victoria Street
Macclesfield
Cheshire
SK11 6LP
UNITED KINGDOM]

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